The Pathogenesis of Subacute Bacterial Endocarditis

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THE first clear reference to the sub-acute form of bacterial endocarditis was made by Senhouse Kirkes in 1852. Osler, in the Goulstonian lectures of 1885, was the first to give a really comprehensive picture of the disease, using the title "Malignant Endocarditis." He was particularly impressed by the frequency with which it was associated with rheumatism or chorea, and by the number of cases in which there had been previous damage to the cardiac valves.

This relationship is one which has been noted over and over again by almost all workers who have studied the disease. There is general agreement that in about fifty per cent. of the cases there has been a previous history of rheumatism. In post-mortem material the evidence is even greater, over eighty per cent., according to some authors. Of those cases with no apparent rheumatic basis, congenital cardiac malformations are noted in many instances. Others, though few in number, present evidence of syphilitic or atherosclerotic changes in the valves. In still others there is no relevant clinical history or underlying valvular change.

The congenital abnormalities most frequently associated with bacterial vegetations are patent ductus arteriosus and bicuspid aortic valve. Lewis and Grant (1923) were the first to recognise clearly that a bicuspid aortic valve may be an acquired rather than a developmental lesion. Gross (1937), and more recently Koletsky (1943), have made intensive histological studies of hearts showing this abnormality. Both these authors noted that in adults, as opposed to children, the affected valves show obvious thickening and fibrosis and are rarely associated with other congenital defects. Koletsky made the further generalisation that in infants and children bicuspid aortic valves are apparently not susceptible to bacterial disease. Both he and Gross formed the opinion that in many instances (forty to fifty in Koletsky's series) the lesion is acquired, generally as the result of a rheumatic valvulitis. In other cases where there is a true congenital defect, care must be taken to exclude a superimposed rheumatic infection. In the post-mortem records of the Royal Victoria Hospital are five cases of subacute bacterial endocarditis occurring in congenitally malformed hearts. Two of these also show the presence of rheumatic stigmata. Equal care in this respect is required in the heart, which is the site of a syphilitic valvulitis. It is emphasized, both from the literature and personal studies, that the examination of only one routine heart block is insufficient evidence for the exclusion of rheumatic stigmata. The available evidence thus suggests that the role of rheumatic carditis in the ætiology of subacute bacterial endocarditis is of even greater importance than generally recognised.

The important question appears to be the mechanism by which the diseased valve favours the deposition of organisms. Some of the older writers believed that

infection occurred as a result of embolisation of the vessels in the scarred valves. The modern idea is that localisation occurs on the valvular surface. The mechanisms suggested are many and varied. Some depend on the interpretation of the ætiology of rheumatic fever itself. Thus Poynton (1920) and others believed that both diseases were bacterial in origin, and that ulcerative endocarditis was "malignant rheumatism." Schlesinger (1935) suggested that rheumatism is a virus disease which predisposes the valves to secondary bacterial invasion. Others consider that it is the structural alterations, such as roughness and calcification, which are of importance. Allen (1939) considers the question of localisation to be dependent on mechanical factors. He believes that in rheumatic valvular deformities, the force of impact, and the duration of contact, of the infected blood with the surface of the valve are increased, and that the brunt of this impact is borne by the line of closure. In the majority of cases of congenital abnormalities Allen considers that there is an obvious self-explanatory defect in mechanics whereby abnormally great tension and impact are transmitted to a region not designed for their reception. The exception is the bicuspid aortic valve. He too considers that in many cases this is an acquired lesion, and that as such valves are fibrosed and deformed, the principles of increased impact and contact are applicable to them. The evidence presented is convincing, but Allen himself emphasizes that his theory attempts to explain, not why implantation occurs, but why it occurs at a particular site. He feels that in all probability localisation takes place after the stage has been set by a generalised altered reaction of tissue or immunity. The latter suggestion is supported by Held and Lieberson (1943), who attribute the peculiar pathological changes and clinical course of subacute bacterial endocarditis to local tissue re-activity caused by hyper-immunity. They suggest that in chronically diseased valves the usual responses to infection do not occur. Instead there is a deposition of fibrin and blood platelets, which constitute the soil on which circulating bacteria implant themselves.

Though not suggesting a similar mechanism for their formation, the presence of such platelet thrombi on diseased valves was noted by Grant, Wood and Jones (1927-9). They found the thrombi particularly frequently on those valves most prone to develop bacterial endocarditis. Their belief is that they occur in response to changes in the underlying valve. They feel that they have demonstrated that it is these platelet thrombi, rather than the crevices and pockets of the scarred valves, which are of importance in bacterial localisation.

Gross and Fried (1937) described a peculiar eosinophilic necrosis of collagen, which they consider to be particularly apt to occur at the line of closure of old rheumatic valves, and in those showing sclerosis of the Mönckeberg type. They also found proliferative changes in the valvular endothelium. These were most marked at those sites which are subjected to the greatest pressure. They believe that it is these valvular changes which predispose to the surface deposition of material from the blood stream, leading to the occurrence of thrombi. These, in turn, act as foci for the implantation of bacteria from the circulating blood. These authors made a study of forty-two cases of subacute, and twenty-eight cases of acute, bacterial endocarditis. Evidence of a previous rheumatic process was found

in seventy-five per cent. They did not consider activity of the rheumatic infection to be a necessary precursor to the development of the bacterial lesions.

This is entirely contrary to the findings of Pappenheimer and von Glahn (1935). They claim to have demonstrated that subacute bacterial endocarditis, rather than attacking valves with old healed lesions, develops on valves bearing recent rheumatic vegetations, and during the existence of active though sub-clinical rheumatism.

From this survey of the literature it has been possible to draw several conclusions. The areas on which vegetations develop have generally been the site of a previous pathological process. In a small number of cases this has been congenital or syphilitic in type. In the vast majority, the underlying lesion has been a rheumatic carditis. In this latter group must be included many of the bicuspid aortic valves seen in adults, which were formerly believed to be congenital in origin. In valves already involved by any of these lesions mechanical factors are important in dictating the site of bacterial localisation. The evidence available suggests that vascular embolisation plays no part in the latter. It is believed that localisation is dictated by changes on the surface of the valve. These surface lesions develop in response to the underlying pathological process, whether congenital, syphilitic, or rheumatic. The nature of these changes, the mechanism of their production, and in particular their relation to rheumatic fever, are all problems which require further elucidation.

With this object in mind, a study was made of the valves of twelve patients dying during an acute attack of rheumatic fever. Many showed evidence of previous attacks, so that varied stages of the rheumatic valvulitis were seen. The findings are in general agreement with those of McKeown, published elsewhere in this Journal. Only those changes considered relevant to the initiation of the bacterial vegetations will be discussed here.

The initial lesion appeared to be a deep valvulitis, possibly spreading from the valve rings to the more distal parts of the leaflet. In its most acute form the valvulitis consisted of a generalised non-specific swelling and œdema, and infiltrations by leucocytes and large mononuclears (plate 1). Later, Aschoff bodies—the specific lesions of rheumatic infection—appeared. These consist of necrosis of collagenous tissues and aggregation of the peculiar large mononuclears known as Aschoff cells. The latter were arranged either as nodules or as a more diffuse reaction. The lesions were most marked in the spongiosa of the mitral valve. When such a reaction occurred deep in the valvular tissues, the appearances and evolution were analogous to those which occur in the myocardium. There were no surface changes with these deeply situated lesions. When intermediate in depth, the rheumatic nodule was often associated with swelling and infiltration of the sub-endocardial tissues on its superficial aspect, so that a cellular "palisade" was formed (plate 2). In other cases there was no true palisade, but merely a "bristling" of the surface layer of cells, which were usually swollen and prominent. In even more superficial Aschoff lesions there was no intervening cellular reaction, so that the necrosis extended to the surface, from which the swollen and œdematous

material often projected as a definite nodule (plate 3). Such areas were sometimes covered by intact endothelium (plate 4). More often the endothelium was either degenerate or had disappeared (plate 5). No other essential difference could be found between the two types, though the areas which had lost their endothelial covering often projected as definite verrucæ. Sometimes such an area was covered by a thin deposit of platelets and sometimes there was also a layer of fibrin (plate 6). On the deeper aspect the typical rheumatic cellular reaction was readily seen.

In view of these findings, the suggestion is made that the rheumatic verruca consists essentially of necrotic collagenous material derived from the valve itself. Deposition of platelets and/or fibrin may occur as an epiphenomenon, but is not the initiating factor. Given the presence of a rheumatic lesion, two processes are concerned in the evolution of the actual verruca. Firstly, œdema and the seepage of fibrin into the necrotic material through the thin covering layer. This may be due to increased permeability of the valvular endothelium, such as is known to occur in damaged capillary endothelium anywhere in the body. Secondly, trauma and mechanical factors, resulting from closure of the swollen valve leaflets, may increase the tendency to protrusion. In this connection it may be noted that microscopic verrucæ were observed on various parts of the valve surface. Macroscopically the characteristic feature of the lesions is that they occur specifically along the line of closure. The explanation may well be that, provided there is present a minute verruca composed of necrotic tissue on the line of closure itself, the traumatisation occuring along this line will favour the deposition of platelets and fibrin. The result will be a verruca readily visible on naked-eye examination. This would account for the more frequent occurrence of the verrucæ on valves where the pressure is greatest, and along the line of closure of such valves.

Two further types of surface necrosis were noted. In one there was an underlying diffuse type of infiltration of the sub-endocardial tissues associated with the presence of cells of the Aschoff type. In the second there was no reaction in the adjacent tissues, but merely a linear superficial collagenous necrosis. A somewhat similar series of surface changes in relation to alterations in the deeper layers of the endocardium was noted in the wall of the left auricle. In lesions regarded as being of longer duration there was often a persistence of the necrotic material after the active cellular reaction had been replaced by granulation tissue. Eventually healing by fibrosis and vascularisation of the valve occurred.

Though not of primary importance in the rheumatic process per se, it was felt that the verrucæ characteristic of its active phase might be the decisive factor in the pathogenesis of bacterial endocarditis. They present a raw area to which any circulating element might readily adhere. That this occurs in the case of platelets and fibrin has already been indicated. The resulting thrombus must surely provide an excellent site for bacterial implantation. With these facts in mind, a study was then made of the valves of thirty-four cases of subacute, and twelve cases of acute, bacterial endocarditis. In many of these the only valves available were those showing massive bacterial vegetations. In them the extent of the latter was often such as to mask any underlying rheumatic lesion. Nevertheless, in eight out of

the thirty-four subacute, and three out of the twelve acute cases, typical rheumatic, bacteria-free vegetations of one or other of the types previously described were seen. A similar observation was made by Gross and Fried (1937). They considered that since the incidence of typical rheumatic verrucæ was lower than that of myocardial Aschoff bodies, and since they were unable to demonstrate even the presence of Aschoff bodies in all cases, they could not conclude that bacterial infection of the valves in rheumatic patients is due to the implantation of bacteria on unhealed rheumatic verrucæ. Nor did they consider that one is justified in interpreting all such verrucæ as evidence of an active rheumatic process. Their explanation was that, as a result of toxic irritative effects of the bacterial infection, non-bacterial verrucæ may form on the valves. If the suggestion be justifiable that the development of verrucæ is dependent not only on the mere occurrence, but also on the site, of the rheumatic valvular lesion, then one would expect the incidence of verrucæ to be lower than that of the incidence of myocardial Aschoff nodules.

With regard to Gross and Fried's hypothesis of the bacterial origin of such vegetations histologically identical with those of rheumatic endocarditis are found: Secondly, all the cases examined by them were examples of bacterial infection, and if the latter is capable of producing a bacteria-free vegetation, one would expect to see a relatively high incidence of such lesions. On their own showing, this was not so. Conversely, Pappenheimer and von Glahn (1935) noted that bacteria-free vegetations histologically identical with those of rheumatic endocarditis are found:

(a) On the same valves as the bacterial vegetations.

(b) On other valves, in the same heart on which there are no vegetations containing organisms.

(c) On the left auricular wall.

They expressed the view that active rheumatic vegetations are, in persons who have had rheumatism, a necessary and almost constant prerequisite for the implantation of bacteria. It has already been shown in the present study that typically rheumatic, bacteria-free vegetations were seen in hearts showing bacterial endocarditis. It is believed that the former are the sites of implantation of the organisms. It is further believed that transitional forms were seen, in which the original localisation of the organism to the fully developed typical bacterial vegetation could be followed. At first there is merely the deposition of a few organisms on the surface of the rheumatic verruca. As the lesion progresses, these organisms multiply, and there is marked deposition of fibrin and platelets. Often, at a slightly later stage, there appears to be a further process of bacterial implantation and multiplication, and the accumulation of more fibrin. In the early stages the rheumatic nature of the underlying lesion is quite clear. With time and the evolution of the bacterial infection this specifically is lost, and the base of the vegetation consists of granulation tissue (plates 7-10).

In order to assess the likelihood of a patient with an acute rheumatic valvulitis developing an infected vegetation, it is necessary to make some estimate of the frequency with which organisms may enter the circulation. The procedures found

by various workers to result in at least a temporary bacteræmia are shown in Table I.

The most comprehensive reports are those of Okell and Elliott (1935). They obtained positive cultures following dental extractions in seventy-five per cent. of cases with marked oral sepsis. In general, they found that the incidence of bacteræmia depended on the degree of sepsis and amount of operative trauma. One of their most significant observations was that in ten per cent. of 110 persons with gross dental sepsis organisms were recoverable from the blood before any operative interference. Murray and Moosnick (1941) showed clearly that the organisms recovered from the blood in such cases are in fact derived from the gingival area. Fish and MacLean (1936) demonstrated streptococci in the blood and lymph spaces in the peridontal membrane and pulp of pyorrhetic teeth. They were able to prevent infection of the blood stream by cauterisation of the gingival area before extraction.

It is thus clear that focal sepsis, particularly of the oral region, may frequently result in bacterial invasion of the blood stream. Before attempting to correlate such bacteræmias with the onset of subacute bacterial endocarditis, one must determine whether the organisms concerned are the same in both instances. In most cases of endocarditis the organism found is a relatively non-pathogenic streptococcus of the viridans type. Most of the remainder are due to the bacillus influenza. Of thirteen cases in the present study giving positive blood cultures, eleven were due to the streptococcus viridans. One yielded a hæmophilus para-influenzæ, and the other a hæmolytic streptococcus.

Rosebury (1944) states that streptococci of the viridans type are generally, though not always, the organisms found in the blood stream in cases with transient bacteræmia. He also states that the most complete serological classification of the greening streptococci is that of Solowey (1942), who studied over two hundred strains. Of these, 108 had been isolated from the blood of patients with endocarditis lenta; 99 were obtained from human throats and infected teeth, 15 were vaginal in origin. No less than three-quarters of these, other than those of vaginal origin, were streptococcus salivarious. In this connection it may be mentioned that Horder (1908-9) found that in sixty-six per cent. of forty cases of subacute bacterial endocarditis, blood culture yielded "saprophytic" streptococci of the type common in the alimentary tract.

Hadfield and Garrod (1942) state that the organism responsible for most cases of subacute bacterial endocarditis is a non-pyogenic streptococcus. In their opinion such organisms exhibit almost endless variety in morphology, colonial characters, and fermentation : they consider that the disease may, in fact, be due to any of a number of nondescript streptococci whose normal habitat is the mouth. They suggest a similar origin for the other accepted causal organism, the hæmophilus para-influenzæ. It thus seems apparent that the organisms concerned in both transient bacteræmias and ulcerative endocarditis of the subacute type are the same.

Recently there have been several reports linking chronic focal sepsis, with the

ever-present opportunity for bacteræmic episodes, with the initiation of infected cardiac vegetations in susceptible patients. Rushton (1930) was one of the first to note this association. He also pointed out that the relation to oral sepsis may often be overlooked, due to omission of any dental examination from the case reports. This is probably true also of many other possible antecedent causes of bacteræmia, which may often be subclinical in their manifestations. Another factor which renders difficult the association of a possible bacteræmic episode with subacute bacterial endocarditis is the very insidious onset of the latter, which makes it difficult to date with accuracy.

It has already been concluded that acute rheumatic valvulitis offers a suitable focus for the implantation of bacteria. The chances of a coincident bacteræmia at this stage appear to be such as to render the superimposition of an infected vegetation a practical possibility.

Corroborative evidence of the importance of activity of the rheumatic process was afforded by study of the myocardial lesions of cases of bacterial endocarditis of the subacute type. Twenty-seven out of thirty-four (seventy-nine per cent.) showed recent rheumatic stigmata of various types. Similar findings were obtained in several of the acute cases. An even more significant finding was that in those cases in which the clinical duration of the bacterial endocarditis could be estimated, the apparent histological age of the rheumatic lesion was comparable.

Moreover, it was demonstrated that the administration of horse-serum to rabbits resulted in myocardial and valvular lesions very similar to those of acute rheumatic carditis in man. In animals showing these lesions the intravenous innoculation of a culture of streptococcus viridans resulted in the development of a bacterial endocarditis of the subacute type. In a control series of normal rabbits receiving an exactly similar dosage of organisms, no evidences of bacterial localisation was found (MacIlwaine, 1945).

This theory of active rheumatic lesions as the ætiological basis for subacute bacterial endocarditis is in accord with many of the recognised features of the disease. The valves on which the bacterial vegetations are prone to develop are those on which the incidence of rheumatic lesions is maximal. Mural implantation of bacteria is uncommon except on the posterior wall of the left auricle. This is a very common site of rheumatic lesions (plate 11). Changes in the valve angle are occasionally noted in rheumatic endocarditis (plate 12). These were also seen in the experimental reproduction of the valvular changes. Both in man and in the rabbit bacterial vegetations were occasionally noted in this situation. None of the other hypotheses suggested for the initiation of the bacterial lesion appear to explain the occurrence of the vegetations on either the left auricular wall or the valve angle, where mechanical stresses are minimal. Clinically, the onset of bacterial endocarditis is unusual in cases with long-standing valvular lesions or in whom auricular fibrillation has supervened. This is interpreted as being due to the fact that the tendency to recurrence of the rheumatic attacks diminishes with increasing age.

In addition, the pathological process described can be utilised to explain at least in part the curious paradox of a comparatively innocuous organism, such as

the streptococcus viridans, as the cause of a disease which is almost, if not always, fatal.

It has been pointed out that the rheumatic verrucæ often show a surface deposition of fibrin, on which it is believed that the organisms settle. The process is regarded as being cumulative, with the laying down of more fibrin and organisms, till finally the large vegetation typical of subacute bacteria endocarditis is formed. The streptococcus grows luxuriantly in fibrin. Friedman (1938) pointed out that a fibrin mass is very impermeable, and that this impermeability is augmented in the presence of serum. He noted that "an infected fibrin mass suspended in serum is the actual pathological picture encountered in subacute bacterial endocarditis." He and his associates believed that persistence of the organisms depends on two factors—

1. The sluggish inflammatory reaction of the valve, so that the focus is not sterilised and walled off, as occurs in other parts of the body.
2. The presence of the fibrin, which not only acts as an excellent culture medium, but also prevents leucocytic infiltration.

The organisms also seem to be unaffected by specific antibodies, which are frequently present in the blood during the course of the disease. This is possibly because they too are unable to pass the fibrin barrier to reach the organisms. The persistence of the infection cannot be attributed to a general lowering of resistance and septicæmia. This is evident from the fact that when particles of the vegetations break off to form emboli, the resulting infarcts are not septic, and heal rapidly. Also, reports in the literature indicate that when it is possible to isolate the infected focus, cure often results. Hamman and Reinhoff (1935) reported a case in which a traumatic arterio-venous aneurysm became the site of an infected vegetation. Complete cure of the viridans septicæmia followed ligation of the affected vessels. There have also been an increasing number of reports in recent years, showing that bacterial endocarditis associated with patent ductus arteriosus has been cured by ligature of the infected segment of the vessels.

The factor responsible for the continuance of the infection must therefore be inherent in the valvular lesion itself.

Many workers, but in particular Libman (1923), have emphasized that healing may occur. This is noted in two types of patient. One is the person who, from showing all the clinical signs and symptoms of the fully developed disease, gradually returns to comparatively normal health. In the second, more common variety, the patient though showing a remission of infection, dies as the result of mechanical alterations in the general circulation, or of embolisation, or even uræmia. At post-mortem of such patients Libman states that there are often evidences of healing.

A point which appears to be of importance in this question of progression or retrogression of the valvular lesion, and which has been relatively neglected in the literature, is the possibility of re-infection. It has been shown that focal sepsis may result in a bacteræmia. Chronicity is usually one of the outstanding features of any focal area of infection. If one bacteræmic episode can occur, there seems

no reason why the process should not be repeated. The large rough bacterial vegetation, with its superficial coating of fibrin, surely presents an even more favourable site for bacterial invasion than the original rheumatic lesion. If this is so, then one can visualize a cumulative process in which the very presence of the bacterial vegetation is the dictating factor in its persistence. Obviously in such circumstances any attempt at healing by the formation of granulation tissue in the base of the vegetation will be frustrated by the superficial deposition of new zones of bacteria and fibrin.

It is felt that this hypothesis may account for those cases in which definite remissions, with obvious improvement in the clinical condition, are followed by the return of all the signs of infectivity, with a fatal termination. When the original and re-infecting organisms are the same, this sequence of events will be almost impossible to prove. There are, however, scattered reports in which re-infection with a different organism has been demonstrated.

Libman (1923) stated that in cases of subacute streptococcal endocarditis, secondary infections with pneumococci are occasionally found. He also noted that following a bacteria-free phase in a case of influenzal endocarditis, re-infection with an anhæmolytic streptococcus occurred. Libman felt that such recurrences of the disease are much more frequent than recognised. Orgain and Poston (1942) presented six cases of classical endocarditis in which two or more organisms were repeatedly isolated from the patient's blood during life.

Although the presence of mixed infection has been noted by several authors, there has been very little comment on this finding. Obviously such an occurrence is of importance, not only in the maintenance of the valvular lesion, but in the therapy of the disease. The main difficulty in effective use of chemotherapeutic agents is generally considered to be the presence of the impermeable fibrin mass which surrounds and protects the bacteria. It has been suggested that heparin may be effective in dissolving this barrier. The reports on sulphonamide therapy, with or without the additional use of heparin, are conflicting, but on the whole disappointing. Some of the reports on penicillin are more promising, but it is too early yet to assume that a reliable and constant therapeutic measure has been found. No bactericidal agent capable of use in the human subject has yet been proved effective against every organism. Therefore, even if some method is found which is universally effective even in the presence of the fibrin barrier, the ultimate test of its value will be whether the organism—or organisms—concerned be susceptible to its action. The recognition of mixed infections thus becomes of practical importance in the treatment of subacute bacterial endocarditis. It is suggested that until the cure of the bacterial lesions becomes a practical reality, chemotherapeutic and other measures should be used in the elimination of all chronic foci of infection elsewhere in the body. These appear to be the initial cause of the bacteræmias without which bacterial endocarditis could not develop, no matter how susceptible the state of the valve. It is wished to emphasize particularly that such prophylactic measures are appropriate in the rheumatic patient. In the absence of a bacteræmia the acute rheumatic valve progresses through the various stages

TABLE I

REPORTED OCCURRENCE OF BACTERÆMIA.

AUTHORS	PROCEDURE
OKELL AND ELLIOTT (1935)	Extraction of teeth.
BURKET AND BURN (1937)	Extraction of teeth.
PALMER AND KEMF (1939)	Extraction of teeth.
MURRAY AND MOOSNICK (1941)	Extraction of teeth.
FAILLO (1942)	Extraction of teeth.
NORTHRUP AND COWLEY (1943)	Extraction of teeth.
ROUND, KIRKPATRICK, AND HAILS (1936)	Ten minutes mastication in patients with pyorrhœa.
ELLIOTT (1939)	Movements of a tooth in its socket before extraction.
MILLET AND VAN EYEK (1940)	Operation or curettage for chronic tonsillitis or enlarged adenoids in children.
ROMER (1913)	Uterine curettage.
RICHARDS (1920)	Manipulation of arthritic joints.
BROWN (1923)	Appendectomy.
SIEFERT (1925)	Various surgical procedures.
LEHMAN (1926)	Uterine curettage.
SCOTT (1929)	Operations on the urinary tract.
BARRINGTON AND WRIGHT (1930)	Operations on the urinary tract.
RICHARDS (1932)	Manual massage of infected areas.

of healing to fibrosis, and the end result is often a well-compensated valvular lesion. If, on the other hand, bacteria enter the blood stream in the active stage of a rheumatic valvulitis, the end result may well be a fatal bacterial endocarditis.

Further, the evidence suggests that waves of bacteræmia may lead to the additional deposition of bacteria in the vegetations. If so, then it becomes a matter of some importance to eradicate all foci of infection, even in the patient who is already suffering from bacterial endocarditis. It is clear that it is of little avail to sterilise the blood stream, or even the vegetations, if new bacteræmic episodes are permitted to occur before there has been time for healing. Until re-epithelialization of the valvular surface is complete, the possibility of re-infection remains. It therefore seems imperative that treatment should be maintained long after the signs of infectivity have disappeared.

CONCLUSIONS.

1. The changes occurring in the valves in the acute stage of rheumatic fever are shown to be of such a nature as to afford a suitable site for the implantation of organisms on a purely mechanical basis.
2. The vegetations of subacute bacterial endocarditis may be associated with typical rheumatic verrucæ.

3. Early implantation of organisms on rheumatic verrucæ has been observed.
4. The sites of bacterial vegetations in the subacute type of endocarditis are identical with those upon which the surface endocardial changes are maximal in rheumatic fever.
5. Bacteræmias, originating from focal sepsis, most commonly in the oral region, are not infrequent. They appear to supply the organism responsible for the majority of cases of subacute bacterial endocarditis.
6. Indications relative to the treatment of this disease in the light of these findings are discussed.

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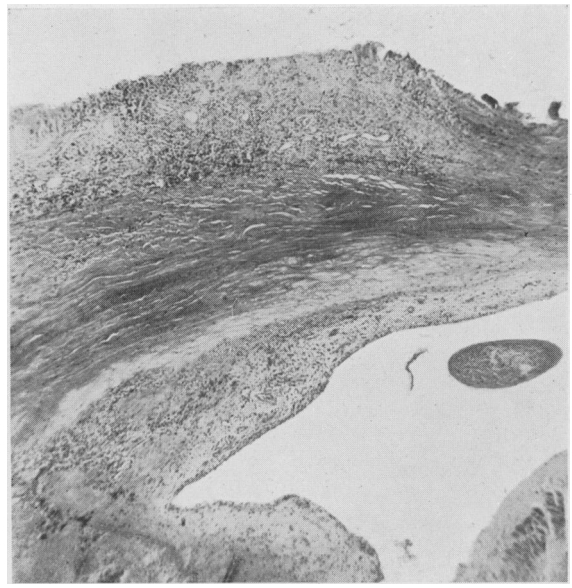

Plate 1. A.2514 (x30)

Acute rheumatic fever. Valve leaflet showing generalised inflammatory infiltration in both layers of spongiosa. The fibrosa is relatively unaffected.

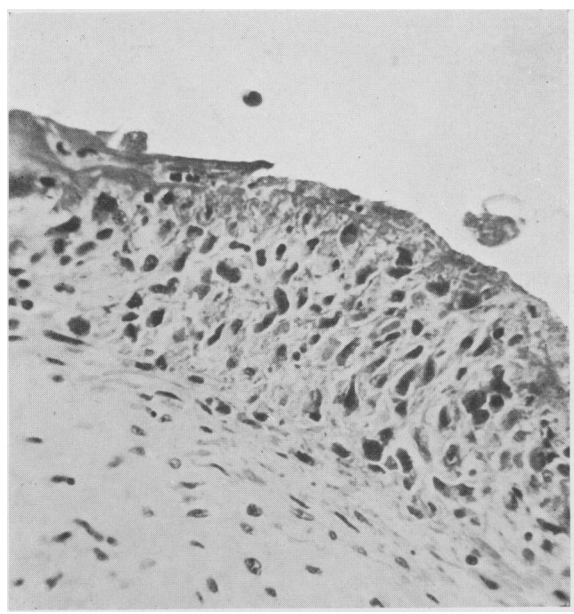

Plate 2. A.4119 (x350)

Rheumatic valvulitis. Palisade arrangement of subendocardial cells. The necrosis of collagen extends through the palisade, and is continuous with surface necrosis.

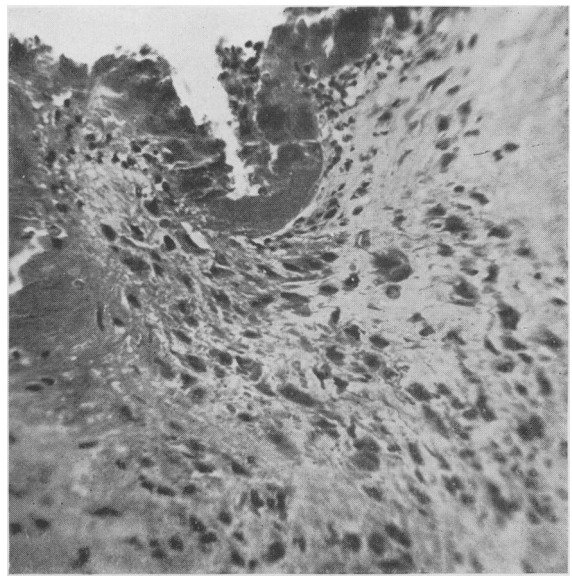

Plate 3. BA.283 (x275)

Rheumatic valvulitis. Marked surface necrosis of collagen. In the deeper layer the specific rheumatic nature of the reaction is shown by the presence of large mononuclears and giant cells.

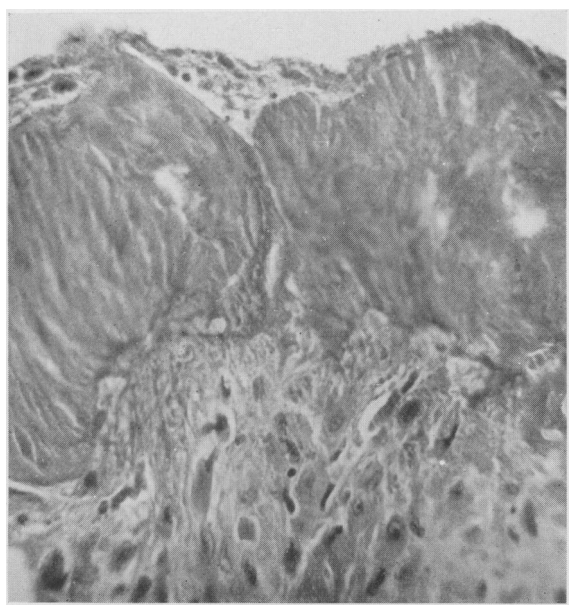

Plate 4. A.3286 (x350)

Typical rheumatic verruca composed entirely of necrotic valvular elements and possibly fibrin, which has entered by seepage. The covering endothelium is still present.

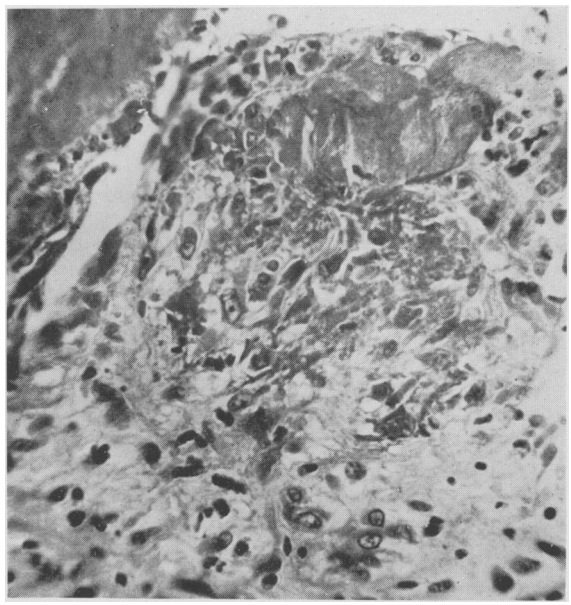

Plate 5. A.4119 (x350)

Rheumatic fever. Superficial necrosis of collagen extending to surface of valve. There has been loss of the covering endothelium.

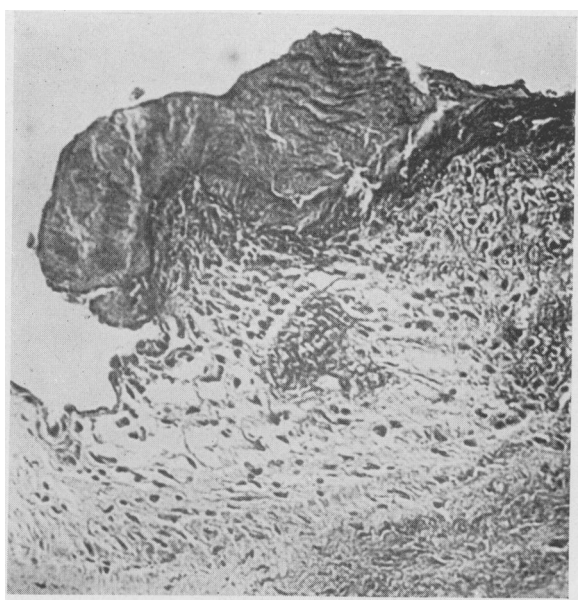

Plate 6. A.4339 (x200)

Rheumatic valvulitis. Verruca projecting from surface of valve and showing superficial deposition of fibrin. There is an underlying rheumatic reaction.

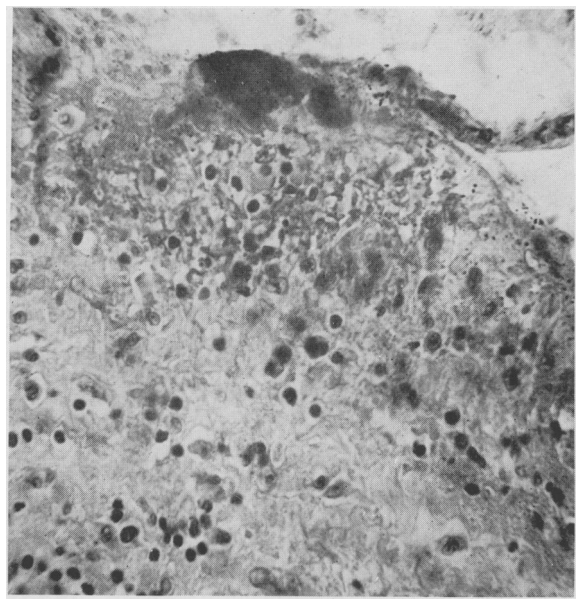

Plate 7. A.2519 (x60)
Early deposition of organisms on surface of active rheumatic lesion.

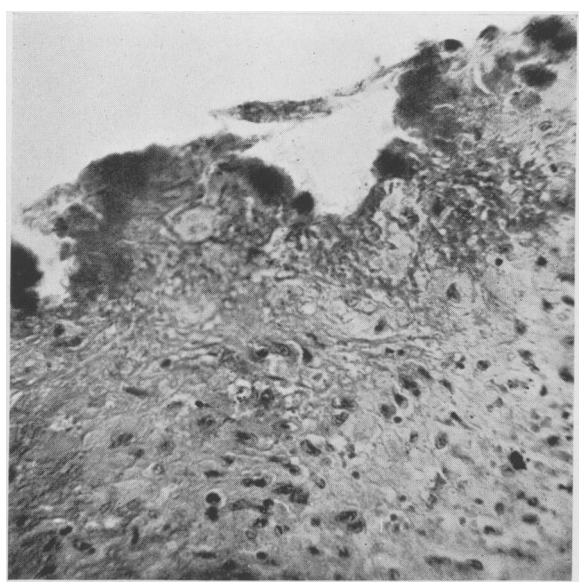

Plate 8. L.4 (x325)
Bacteria implanting on necrotic collagen along surface of mitral valve. The deeper layers show the rheumatic type of reaction.

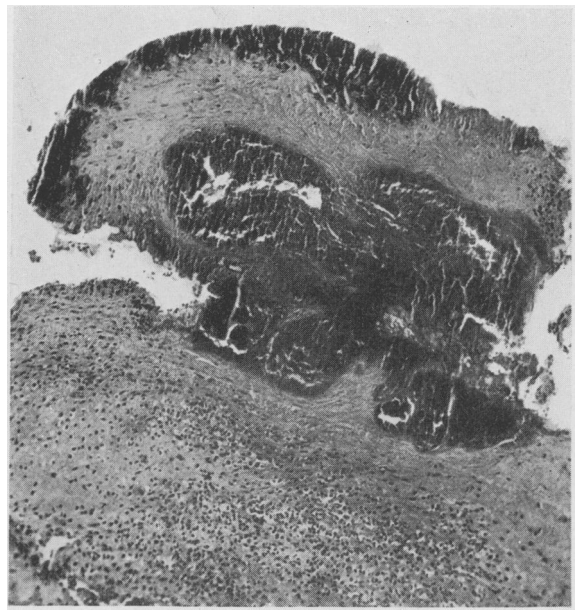

Plate 9. A.2519 (x120)

Later stage in the evolution of the bacterial vegetation. The organisms have multiplied within their protective covering of fibrin. On the outer aspect of the fibrin there is another zone of bacteria.

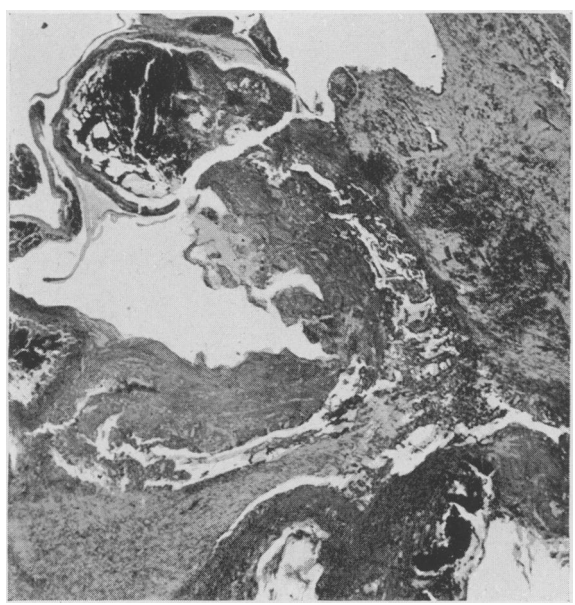

Plate 10. A.2703 (x20)

Part of large fully-developed bacterial lesion.

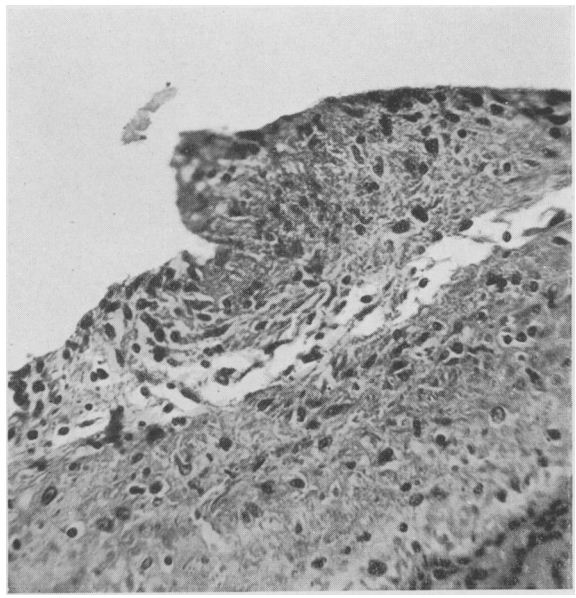

Plate 11. A.2699 (x275)
Rheumatic lesion in left auricular endocardium.

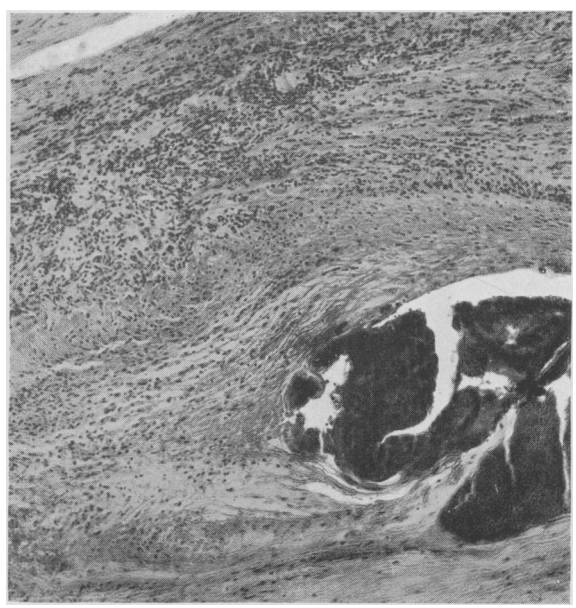

Plate 12. BA.283 (x100)
Intense necrosis of collagen in valve angle in acute rheumatic valvulitis.